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February 4, 2002

The Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on DuPont's HPV Test Plan and Robust Summary for 4,4-Oxydianiline

Dear Administrator Whitman:

The following comments on the DuPont test plan for 4,4-oxydianiline are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than nine million Americans.

DuPont's test plan calls for a developmental toxicity test with oxydianiline, which will kill 240 animals. DuPont is proposing to conduct this test despite the fact that numerous experiments already indicate that oxydianiline, as well as similar aromatic amine compounds, cause a wide range of tumors in different species. Human exposure to this chemical is also associated with serious acute and chronic adverse health effects, including cyanosis and cancers. Further testing on animals will not expand the understanding of the toxic effects with this chemical, and, therefore, any additional testing on animals is inappropriate and unnecessary. This test plan violates the October 1999 agreement among the EPA, industry, and health, animal protection, and environmental organizations, which state, in part:

1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.

8. As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.

Oxydianiline, an aromatic amine, is used to produce straight polyimide resins. These resins resist high temperatures and are present in wire enamels, coatings, film, adhesives, insulating varnishes, coated fabrics, and machine parts.

Aromatic amines comprise a group of chemicals that have long been associated with cancer. Extensive data on this chemical are readily available and suggest that different species of animals develop tumors after being dosed with this chemical. Studies suggest that oxydianiline causes tumors across sexes, across species, and at multiple target sites. The bladder is recognized as the major site in humans, while many rodent studies indicate that oxydianiline causes hepatocarcinogenicity in animals. This chemical has also been shown to be mutagenic in many *in vivo* and *in vitro* studies. The International Agency for Research on Cancer (IARC) has

classified oxydianiline as 2B, a possible human carcinogen. The preponderance of evidence suggests that this chemical is toxic, mutagenic, and carcinogenic, and no further tests on animals should be conducted.

Mice fed oxydianiline develop hepatocellular adenomas, follicular cell adenomas, and adenomas of the Harderian gland. Rats dosed orally with oxydianiline also develop liver tumors and have an increased incidence of thyroid follicular cell adenoma. Rats or mice given subcutaneous or intramuscular injections of oxydianiline develop tumors at multiple sites, but particularly in the liver. Other chronic toxic effects include kidney injury, parenchymatous goiter, and pituitary hyperplasia.

Anilines also present acute hazards. Like aniline, oxydianiline is associated with formation of methemoglobin in the blood, potentially resulting in cyanosis or methemoglobinemia. Tachycardia, dyspnea, and tachypnea may also occur. Associated CNS effects include headache, dizziness, altered mental status, and confusion.

There is no justification for subjecting more animals to test oxydianiline. Rather, DuPont should ensure that workers and the communities surrounding its manufacturing sites are not exposed to this toxic compound.

Due to low vapor pressures, respiratory exposure to vapors of most aromatic amines should be low, but inhalation exposure to the solid form is possible. In occupational settings, workers could be exposed to oxydianiline through inhalation of dust and through eye and skin contact. Oxydianile is very reactive and has a short half-life of 1.8 hours. Because of its very short half-life, chronic exposure of prospective parents unlikely. This exposure information provides additional support for elimination of the developmental toxicity test.

In conclusion, the proposed developmental toxicity test is inappropriate and unnecessary. Oxydianiline, an aromatic amine, is associated with severe acute and chronic effects, and is toxic, mutagenic, and carcinogenic in many types of studies on many species. Different species exhibit different effects, and further tests on animals will not expand the understanding of adverse health effects associated with human exposure to oxydianiline. Given the association of this chemical with cancer, chemical manufacturers, processors, and importers should reduce exposures to the lowest level feasible.

The current proposed DuPont test plan comes on the heels of two previous DuPont test plans we commented on in January. Those test plans also proposed a number of irrelevant and unnecessary tests. For example, DuPont had proposed to conduct dermal and eye irritation tests for the dinitrile category. Dupont withdrew these plans after being contacted by People for the Ethical Treatment of Animals (letter dated December 11, 2001, from Edwin Mongan to Jessica Sandler). DuPont is also planning to kill 960 animals to test adipic acid, even though this chemical has been found safe by the Food and Drug Administration for use as a food additive and is used in powdered drink mixes, cheese, and candy. Many animals have already died to test this chemical, and further testing on animals will not provide increased understanding of its effects or change the way in which the substance is handled. These tests violate the letter, as well as the spirit, of the October 1999 agreement, which specifies that thoughtful toxicology should be used and, particularly for GRAS chemicals, tests should not be conducted for information that is not "useful or relevant." We have not yet received any response from either DuPont or the EPA to the two sets of comments we submitted on January 11, 2002.

Thank you for your attention to these comments. I can be reached at 202-686-2210, ext. 302, or via e-mail at *ncardello@pcrm.org*.

Sincerely,

Nicole Cardello, M.H.S.
Staff Scientist